I. STUDY OF THE INTERNAL MANNICH REACTION

II. STUDY OF THE CLEMMENSEN REDUCTION OF FIVE- AND SEVEN-MEMBERED CYCLIC AMINES CONTAINING THE KETONE FUNCTION

BY

ERIC BARTHEL, JR.

B.S., Bradley University, 1943
M.S., University of Illinois, 1947

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY
IN THE GRADUATE COLLEGE OF THE
UNIVERSITY OF ILLINOIS, 1949

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PART ONE

STUDY OF THE INTERNAL MANNICH REACTION

Introduction

This investigation was undertaken to determine if ring closure could be achieved through a Mannich reaction upon a molecule which contained both the amino group and an active hydrogen atom in positions favorable to cyclization. There is no record of a reaction of this type in the literature.

Discussion Of Results

The three compounds studied would lead to known substances if an internal ring closure could be realized through a Mannich reaction. The product obtained from *o*-aminoacetophenone would be 4-tetrahydroquinolone, previously prepared by Clemo and Perkin (1). Diacetoneamine hydrogen oxalate would lead to 2,2-dimethylpiperidone-4 (2) and 1-(α-piperidyl)-propanone-2 would afford 2-ketoquinolizidine (3).

A variety of conditions were used in attempting to achieve cyclization, but in no instance could any of the desired material be obtained. The products were all of polymeric nature, with the exception of several experiments with 1-(α-piperidyl)-propanone-2 hydrochloride and paraformaldehyde, from which the unchanged starting material was recovered.

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PART TWO

STUDY OF THE CLEMMENSEN REDUCTION OF FIVE- AND SEVEN-MEMBERED CYCLIC AMINES CONTAINING THE KETONE FUNCTION

Introduction

It has been shown (1) that the rearrangement of bicyclic α-amino ketones during Clemmensen reduction first noted by Clemo (2) and Prelog (3) takes place with contraction of the ring containing the carbonyl function. By unequivocal synthesis, it has been demonstrated that the product of Clemmensen reduction of 1-keto-2-methylquinolizidine was 8-methyl-1-azabicyclo[5.3.0]decane. Similarly, 1-keto-8-methylquinolizidine yielded 4-methyl-1-azabicyclo[5.3.0]decane. Rearrangement also occurs during Clemmensen reduction of 6-keto-1-azabicyclo[5.3.0]decane to afford quinolizidine (1). Monocyclic α-amino ketones were also shown to rearrange during reduction under Clemmensen conditions; thus, 1-methyl-2-ethyl-3-piperidone yielded 1-methyl-2-propylpyrrolidine (4).

The purposes of this investigation were threefold. The course of the reaction was determined when five- and seven-membered cyclic α-amino ketones were reduced. The influence of substitution on the *alpha* carbon atom was investigated and the reduction of an α-amino ketone in which the carbonyl group was not in the ring was studied.

Discussion Of Results

The amino ketones used in this investigation were synthesized in a manner analogous to that used for the preparation of 1-methyl-2-ethyl-3-piperidone (4).

When subjected to Clemmensen reduction, 1-methyl-2-ethyl-1-azacycloheptan-3-one was rearranged to 1-methyl-2-propylpiperidine. The identity of the product was established by comparison, through melting points and mixed melting

points of various derivatives, with an authentic sample (5). Similarly, 1,2-dimethyl-1-azacycloheptan-3-one afforded 1-methyl-2-ethylpiperidine upon reduction. An authentic sample, obtained by two-step reduction of 2-vinylpyridine, followed by methylation using methyl iodide, was shown to be identical with the Clemmensen reduction product.

Clemmensen reduction of 1-methyl-2-ethyl-3-pyrrolidone yielded at least two products. One of these was shown to be a secondary amine, postulated as being methyl *n*-hexylamine. The other product may be the amino carbinol, resulting from incomplete reduction of the carbonyl function.

The identity of the product of Clemmensen reduction of 1-methyl-3-piperidone, 1,2-dimethylpyrrolidine, was shown through comparison with an authentic sample. Under similar conditions, 1,2,2-trimethyl-3-piperidone yielded 1-methyl-2-isopropylpyrrolidine. Reductive cyclization of methyl γ-nitro-δ-methylhexanoate afforded a specimen of the substituted pyrrolidine for comparison. 1,2-Dimethyl-2-ethyl-3-piperidone was converted to 1-methyl-2-*sec*-butylpyrrolidine during Clemmensen reduction. The results of these three reductions indicate that the alkyl substituent on the *alpha* carbon atom of an α-amino ketone apparently has no affect upon the course of the rearrangement during Clemmensen reduction.

Reduction of 1-methyl-2-acetylpiperidine under Clemmensen conditions yielded a secondary amine. The boiling point of the base and the melting points of the picrate and chloroplatinate serve to identify the material provisionally as methyl *n*-heptylamine (6). Sufficient amounts of these derivatives were not obtained for analysis.

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VITA

The author was born in Lincoln, Illinois, on October 3, 1921. He attended the grade and high schools of that city and was graduated from Lincoln Community High School in 1939. He received the degree of Bachelor of Science from Bradley University, Peoria, Illinois, on April 20, 1943. After serving in the United States Naval Reserve from 1943 to 1946, the author entered the graduate school of the University of Illinois in the summer of 1946. The degree of Master of Science was received from that institution in 1947. He served as an assistant in chemistry from 1946 to 1948. A university fellowship was held from 1948 to 1949 and a grant from the Research Board was received during the summer of 1949.

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